behavior which is also observed here in these solvents.

A point to be raised is the decrease of the reaction order, both in dichloromethane and acetonitrile, as the amine becomes more sterically hindered. This observation also agrees with the postulated schemes. Steric bulk prevents amine association or effective solvation. It also reduces the nucleophilicity of the attacking amine. On the other hand, a bulkier tetrahedral intermediate (T^0 or T^-) collapses faster to products because of steric acceleration. All these effects may cause the initial amine attack on the carbonyl to become slower than the decomposition of the tetrahedral intermediate and therefore to become the rate-determining step. By thus shifting the rate-determining step, sterically hindered amines decrease the rate of aminolysis and the reaction order in RNH_2, in agreement with the postulated schemes.

The fact that the cross aminolysis (*n*-octylamine/*tert*-butylamine) of **1a** in acetonitrile showed a first-order dependence on [*t*-$BuNH_2$], when the *n*-octylamine concentration was kept constant, reinforces the above arguments. The presence of the more reactive octylamine ensures a fast equilibrium between $T^{\pm}$ and reagents. The more hindered *tert*-butylamine can only intervene as a base catalyst in the formation of T^- from $T^{\pm}$ or, alternatively, in the decomposition of T^0. In both cases, a first-order dependence on [*t*-$BuNH_2$] is to be expected, if the rate-determining step is the collapse of the tetrahedral intermediates.

In conclusion, we propose essentially two mechanisms to accommodate our data. In the first one, in solvents like *n*-heptane and dichloromethane, where a third-order dependence on [RNH_2] is observed, the reaction proceeds through a neutral T^0 intermediate, which decomposes to products in a base-catalyzed rate-determining step (route a). In the second, stepwise mechanism (route b), the reaction proceeds through a zwitterionic $T^{\pm}$ intermediate, which is converted by a second molecule of the amine into a T^- intermediate. Collapse of this intermediate is rate-determining. This process takes place in solvents like THF, dioxane, and acetonitrile, where a second-order dependence on [RNH_2] is observed, and amine association is disrupted by solvation through hydrogen bonds with the donor solvent.

The anti-Arrhenius behavior observed in both groups of solvents is explained as arising from contributions from fast exothermic preequilibria to the observed rate constants. In the first mechanism (route a) we agree with Nudelmann and Palleros[12] in regarding the amine association as the source of this contribution. In the second mechanism (route b), a similar argument holds, and the associated amine molecules are replaced by molecules of the better donor solvents.

Experimental Section

Solvents were dried and purified by standard methods. All amines employed were analytically pure and were purified by distillation prior to use. The 2,2,2-trichloro-1-arylethanones (**1**) were prepared following previously published procedures.[7,9] The identificaiton of the product amines was carried out by spectral comparison with authentic samples.[9]

Kinetic runs were carried out utilizing a UV-visible Shimadzu 210-A spectrometer interfaced with a microprocessor. The reactions were run in thermostatted (±0.1 °C) cell compartments, following the disappearance of the K band of the substrates **1a**, **1b**, **1c**, **1d**, and **1e** at 258, 270, 269, 274, and 245 nm, respectively, in the presence of an excess amine, under pseudo-first-order conditions. Each run was automatically scanned for at least 3 half-lives, with an average acquisition of 250 absorbance readings. The pseudo-first-order rate constants were calculated with the aid of an iterative program applied to the acquired data. The constants thus obtained had standard deviations smaller than 1%.

The reaction orders in amine were obtained from plots of log k_{obs} vs log [RNH_2], as the slopes of the corresponding straight lines. The average orders and the standard deviations for all solvents were 3.1 ± 0.3 (*n*-heptane), 3.0 ± 0.1 (dichloromethane), 2.0 ± 0.1 (1,4-dioxane), 2.0 ± 0.1 (tetrahydrofuran), 2.0 ± 0.1 (acetonitrile). Plots of k_{obs} vs $[RNH_2]^n$, where *n* equals 2 or 3, depending on the employed solvent, yielded straight lines with correlation coefficients $r \geq 0.99$.

Acknowledgment. We thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Financiadora de Estudos e Projetos (FINEP) for financial support to this work.

Synthesis of Fused Polyazapolycyclic Compounds through Condensation of Diaminoalkanes with Carbonyl Compounds

David StC. Black, Donald C. Craig, Olga Giitsidis, Roger W. Read,* Abdoreza Salek, and Mark A. Sefton

School of Chemistry, University of New South Wales, P.O. Box 1, Kensington N.S.W. 2033, Australia

Received October 11, 1988

1,3-Diaminopropane and 1,3-diamino-2,2-dimethylpropane react with glyoxal to give crystalline 2,2′-bis(hexahydropyrimidine) derivatives 1 and **2**. Subsequent treatment with formaldehyde and acetaldehyde gives trans- and to a lesser extent cis-fused 1:1 addition products, e.g. 4a,8b-*trans*-2,2,7,7-tetramethylperhydro-4,5,8a,9a-tetraazafluorene (**8**) and 4a,8b-*cis*-2,2,7,7-tetramethylperhydro-4,5,8a,9a-tetraazafluorene (**14**), or tetracyclic cis-fused 1:2 addition products, e.g. 8b,8c-*cis*-2,2,6,6-tetramethylperhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorene (**18**), depending upon the ratio of the reactants and upon reaction conditions. Similar condensation with acetone required mild acid catalysis and gave only the 1:1 addition products. The bis(hexahydropyrimidine) nature of the initial products was confirmed by conversion to their tetranitroso derivatives and by X-ray crystallographic analysis of the tetranitro derivative, 2,2′-bis(1,3-dinitrohexahydropyrimidine) (**5**), of compound 1.

Introduction

The condensation of linear and cyclic tetraamines with glyoxal provides a direct route to monomeric, tricyclic,[1,2] and tetracyclic[3-5] nitrogen heterocycles. Similar tricycles have also been reportedly prepared from linear tetraamines

(1) Fuchs, B.; Ellenzweig, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 326.

(2) Jazwinski, J.; Kolinski, R. A. *Tetrahedron Lett.* **1981**, *22*, 1711.

0022-3263/89/1954-4771$01.50/0

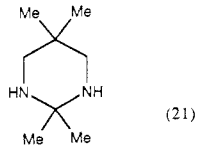
and butanedione.[6] However this method of synthesis is difficult to apply in cases in which the heterocycles have methylene bridges on the periphery. The difficulty arises from the inaccessibility and probable instability of the requisite tetraamine precursors. The synthesis outlined in Scheme I is an alternative approach to two classes of such methylene-bridged heterocycles, the perhydrotetraazafluorene and perhydrotetraazacyclopentanofluorene compounds. The scheme involves preformation of the 2,2′-bis(hexahydropyrimidine) skeleton and subsequent elaboration of the third and fourth rings through condensation with aldehydes and ketones.

Surprisingly, there are few reports of simple 2,2′-bis(hexahydropyrimidine) derivatives in the literature.[2,7,8] The only paper describing structural information of the compounds concerns a study of the rotamer populations of *N,N′,N″,N‴*-tetranitroso-2,2′-bis(hexahydropyrimidine) by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy;[8] to our knowledge, no other structural characterization of molecules of this type has appeared. This paper sets forth spectroscopic and X-ray crystallographic evidence for the structures of model bis(hexahydropyrimidines) **1** and **2**. It also describes the utilization of **1** and **2** in condensation reactions of the type shown in Scheme I and provides strong supporting spectral evidence for the structure of the products.

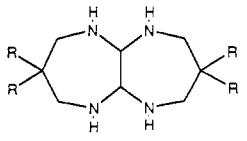
Results and Discussion

2,2′-Bis(hexahydropyrimidine) Derivatives 1–6. Compounds **1** and **2** were obtained in 47% and 75% yields, respectively, through condensation of 1,3-diaminopropane and 1,3-diamino-2,2-dimethylpropane with 40% aqueous glyoxal by modification of a method described for the condensation of 1,2-diaminoethane with glyoxal.[9] No product crystallized from reaction mixtures in which 30% glyoxal was used.

The mass spectra of hexahydropyrimidines **1** and **2** were dominated by base peaks of m/z = M/2, presumably resulting from a facile fission of the C(2), C(2′) bond.[1,10] Each substance showed five types of proton resonances in the ^{1}H NMR spectrum (Table IV), apart from NH signals, as befits symmetrical 2:1 condensation products. Also there were well-defined proton splitting patterns consistent with comparatively rigid structures. The sum of these results pointed to structures **1** and **2** rather than **22** and **23** for the two adducts (see later).



(21)



(22) R = H
(23) R = Me

Table I. Interatomic Distances and Standard Deviations (Å) for 5

C(1)–N(1)	1.450 (2)	N(1)–N(3)	1.380 (2)
N(1)–C(2)	1.464 (2)	N(3)–O(1)	1.215 (2)
C(2)–C(3)	1.508 (3)	N(3)–O(2)	1.219 (2)
C(3)–C(4)	1.511 (3)	N(2)–N(4)	1.355 (2)
C(4)–N(2)	1.472 (2)	N(4)–O(3)	1.224 (2)
N(2)–C(1)	1.449 (2)	N(4)–O(4)	1.216 (2)
C(1)–C(1)[a]	1.546 (3)		

[a] Superscripts refer to the following symmetry transformations: 1-X,1-Y,1-Z.

Table II. Interatomic Angles and Standard Deviations (deg) for 5

N(3)–N(1)–C(1)	116.2 (1)	O(3)–N(4)–O(4)	125.0 (2)
N(3)–N(1)–C(2)	118.5 (1)	O(3)–N(4)–N(2)	117.4 (2)
C(1)–N(1)–C(2)	117.2 (1)	O(4)–N(4)–N(2)	117.6 (2)
N(4)–N(2)–C(1)	118.2 (1)	N(1)–C(1)–N(2)	110.4 (1)
N(4)–N(2)–C(4)	120.7 (2)	N(1)–C(2)–C(3)	111.0 (2)
C(1)–N(2)–C(4)	118.7 (1)	C(2)–C(3)–C(4)	110.0 (2)
O(1)–N(3)–O(2)	125.1 (2)	N(2)–C(4)–C(3)	110.3 (2)
O(1)–N(3)–N(1)	117.4 (2)	C(1)[a]–C(1)–N(1)	108.7 (2)
O(2)–N(3)–N(1)	117.4 (2)	C(1)[a]–C(1)–N(2)	109.7 (2)

[a] Superscripts refer to the following symmetry transformations: 1-X,1-Y,1-Z.

Table III. Torsional Angles and Standard Deviations (deg) for 5

C(1)–N(1)–N(3)–O(1)	22.6 (2)	C(4)–N(2)–N(4)–O(3)	−176.6 (2)
C(1)–N(1)–N(3)–O(2)	−161.0 (2)	C(4)–N(2)–N(4)–O(4)	6.0 (3)
C(2)–N(1)–N(3)–O(1)	170.6 (2)	N(4)–N(2)–C(1)–N(1)	−117.2 (2)
C(2)–N(1)–N(3)–O(2)	−13.0 (2)	C(4)–N(2)–C(1)–N(1)	45.2 (2)
N(2)–C(1)–N(1)–N(3)	102.4 (2)	C(3)–C(4)–N(2)–N(4)	111.8 (2)
N(2)–C(1)–N(1)–C(2)	−46.0 (2)	C(3)–C(4)–N(2)–C(1)	−50.2 (2)
N(3)–N(1)–C(2)–C(3)	−94.9 (2)	N(1)–C(2)–C(3)–C(4)	−54.2 (2)
C(1)–N(1)–C(2)–C(3)	52.7 (2)	C(2)–C(3)–C(4)–N(2)	52.3 (2)
C(1)–N(2)–N(4)–O(3)	−14.5 (3)	N(1)–C(1)–C(1)[a]–N(2)[a]	59.2 (2)
C(1)–N(2)–N(4)–O(4)	168.0 (2)	N(2)–C(1)–C(1)[a]–N(1)[a]	−59.2 (2)

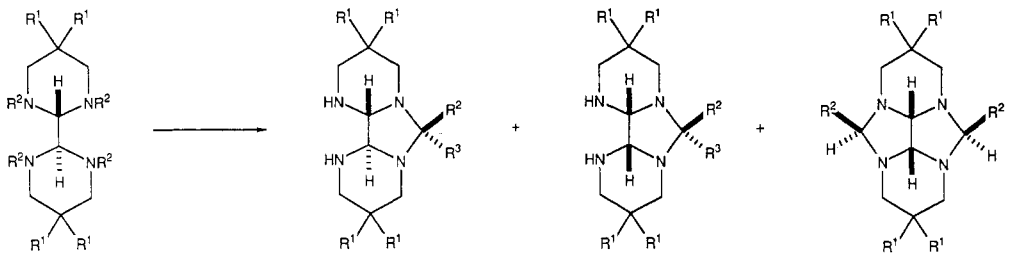
[a] Superscripts refer to the following symmetry transformations: 1-X,1-Y,1-Z.

Supporting evidence for the structures of **1** and **2** was gained by preparation of the tetranitroso derivatives, **3** and **4**, and tetranitro derivatives **5** and **6**. These derivatives were prepared through treatment of **1** and **2** with sodium nitrite in dilute hydrochloric acid[11] and with nitric acid in trifluoroacetic anhydride,[12] respectively. All four compounds were obtained in highly crystalline form.

The tetranitroso derivatives **3** and **4** and tetranitro derivatives **5** and **6** gave satisfactory elemental analyses except for **3**, which was characterized as its hemihydrate. They also showed very small or nonexistent molecular ions in their mass spectra but again gave base peaks of m/z = M/2, consistent with fission of the molecules into halves. The 500-MHz ^{1}H NMR spectra of the tetranitroso derivatives in DMSO-d_6 solution were complex. However, the presence of numerous sharp signals in the region δ 7.5–9.0 was consistent with the existence of different N–NO rotamers. The pattern of these signals for **3** was almost identical with that already described[8] (in the nomenclature used previously: conformer A (18%), B (37), C (23), D_1 (5), D_2 (6), E (9), F (2)) with minor differences in chemical shift possibly due to variations in temperature or concentration. Those signals for **4** suggested similar rotamer populations, A, B, C, D_1, D_2, E, F, in the ratio 21, 37, 15, 7, 7, 11, 2. In contrast, but as expected, the ^{1}H NMR spectra of the tetranitro derivatives (Table IV) did not show the presence of isomeric mixtures. They each showed

(3) Caulkett, P. W. R.; Greatbanks, D.; Turner, R. W.; Jarvis, J. A. J. *J. Chem. Soc., Chem. Commun.* **1977**, 150.
(4) Weisman, G. R.; Ho, S. C. H.; Johnson, V. *Tetrahedron Lett.* **1980**, *21*, 335.
(5) Choinski, W.; Kolinski, R. A. Polish Patent 101,075, March 31, 1979; *Chem. Abstr.* **1980**, *92*, 94444x.
(6) Stetter, H. *Chem. Ber.* **1953**, *86*, 69.
(7) Mark, H. F. (to Aries, R. S.) U.S. Patent 2,895,944, July 21, 1959; *Chem. Abstr.* **1960**, *54*, 16029e.
(8) Willer, R. L.; Moore, D. W. *Magn. Reson. Chem.* **1988**, *26*, 95.
(9) Willer, R. L. *Prop. Explos., Pyrotech.* **1983**, *8*, 65.
(10) Willer, R. L.; Moore, D. W.; Johnson, L. F. *J. Am. Chem. Soc.* **1982**, *104*, 3951.
(11) Kamlet, M.; Jacobs, S. *J. Chem. Phys.* **1968**, *48*, 23.
(12) Fuchs, B. *Tetrahedron Lett.* **1970**, 1747.

Scheme I



	R^1	R^2
(1)	H	H
(2)	Me	H
(3)	H	NO
(4)	Me	NO
(5)	H	NO_2
(6)	Me	NO_2

	R^1	R^2	R^3
(7)	H	H	H
(8)	Me	H	H
(9)	H	Me	H
(10)	Me	Me	H
(11)	H	Me	Me
(12)	Me	Me	Me

	R^1	R^2	R^3
(13)	H	H	H
(14)	Me	H	H
(15)	H	Me	H
(16)	H	Me	Me

	R^1	R^2
(17)	H	H
(18)	Me	H
(19)	H	Me
(20)	Me	Me

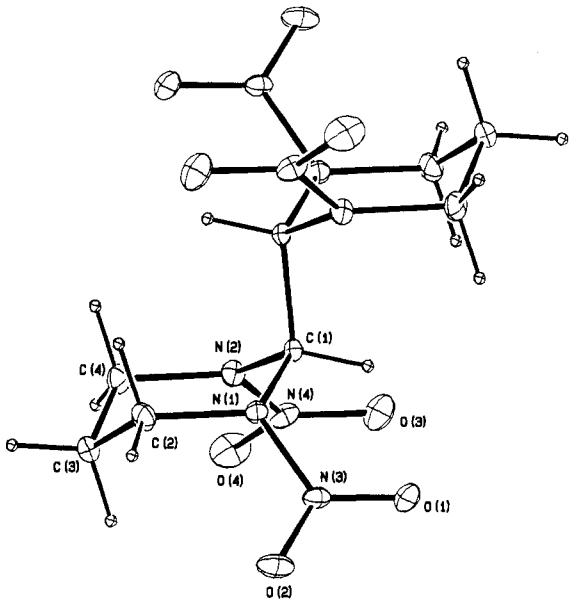


Figure 1. X-ray crystal structure of bis(1,3-dinitrohexahydropyrimidine) (**5**).

five types of protons with well-defined splitting patterns and were fully consistent with stable, highly symmetrical structures resembling those of **1** and **2**.

The tetranitro derivative **5**, after recrystallization from nitric acid, was obtained as colorless plates. Examination of **5** by single-crystal X-ray crystallographic analysis (see ORTEP diagram Figure 1 and Tables I–III) confirmed the presence of two hexahydropyrimidine rings bridged through positions 2 and 2′. Each ring exists in a chair conformation with the bridging hydrogens held in equatorial configurations and twisted with respect to each other into an antiperiplanar relationship. It is interesting that while the rings themselves are very slightly distorted, there is a center of inversion in the interring bond, so that the chair conformations of the two rings are identical. The *N*-nitro groups occupy pseudoequatorial positions, with the planes of the nitro groups subtending small torsional angles of approximately 21° and 13° with respect to the N–C bond to the bridging carbon and 11° and 5° with respect to the N–C bond away from the bridging carbon, respectively (Table III). This suggests the likelihood of considerable second-order bonding between the amine nitrogens and the nitro nitrogens attached. The relatively short N–N bond lengths, 1.380 (2) and 1.355 (2), respectively (Table I), support this possibility, as do the sums of the bond angles about N(1) and N(2), 351.9 and 357.6°, respectively (Table II). The bridging C–C bond is of normal length and therefore not strained. The preferred chair conformation of the rings explains the observed spin–spin coupling pattern seen in the NMR spectrum of **5** (Table IV).

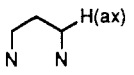
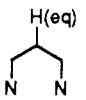
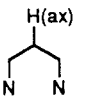
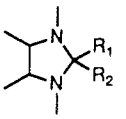
Reactions of Bis(hexahydropyrimidines) 1 and 2 with 1 Equiv of Formaldehyde, Acetaldehyde, and Acetone. The reactions of **1** and **2** with 1 equiv of formaldehyde (as formalin) proved to be complex.

The cleanest reaction of formaldehyde with **1** was obtained after heating a methanolic solution of the reactants to reflux temperature, even though no starting material was in evidence by ^{1}H NMR spectroscopy after reactions involving reaction and workup temperatures as low as −17 °C. Evaporation of the solvent and distillation of the crude product gave a ca. 40% yield of a 4:3 mixture of 1:1-adducts **7** and **13**, as estimated by the ^{1}H NMR spectrum. A small amount of starting material, **1**, was also present. Fractional crystallization gave the major trans isomer **7** and the minor isomer was assigned the cis structure **13** from the NMR spectrum of the mixture.

The addition of 1 equiv of formaldehyde to **2** was carried out under a variety of conditions. Best conditions for the formation of 1:1 adducts were with methanol solutions stirred at room temperature for 1 h. Substitution of paraformaldehyde for formalin did not affect the course of the reaction. Distillation of the crude reaction product gave a 40% yield of distillate, shown by ^{1}H NMR spectroscopy to comprise a mixture of 1:1 adducts, **8** and **14**, in a ratio of 4:1, contaminated with a small quantity of a third substance. Repeated crystallization of the distillate gave a pure sample of the major adduct **8**. The third component was later identified as the bis-adduct **18**.

Both **1** and **2** reacted with 1 equiv of acetaldehyde more cleanly than with formaldehyde to give predominantly the tricyclic compounds; the less substituted bis(hexahydropyrimidine) **1** proved the more reactive of the two. The crude reaction mixture, from **1**, formed in methanol at 0 °C, comprised 75% of the trans 1:1-adduct **9** (^{1}H NMR) together with the 1:2 adduct (**19**). At room temperature and at 60 °C increasingly larger quantities of **19** were formed. The addition of 1 equiv of acetaldehyde to a methanolic solution of **2** at room temperature gave a mixture comprising approximately 80–85% of the trans 1:1 adduct **10**, accompanied by approximately 10% of the 1:2 adduct **20**. The major adducts **9** and **10** were isolated by crystallization from the respective crude reaction products.

Table IV. ^{1}H NMR Spectral Data of Compounds 1, 2, and 5–20

							
1	3.33 (s)	3.11 (ddd, 13.1, 4.4, 2.1)	2.74 (ddd, 13.1, 12.1, 3.0)	1.42 (dd, 13.3, 3.0, 2.1)	1.49 (dtt, 13.3, 12.1, 4.4)	–	–
2	3.36 (s)	2.66 (d, 12.6)	2.55 (d, 12.6)	–	–	0.75 (s) 1.03 (s)	–
5[a]	7.48 (s)	3.86 (ddd, 12.2, 5.8, 2.5)	3.84 (ddd, 12.2, 12.1, 4.6)	2.49 (dtt, 15.4, 4.6, 2.5)	2.28 (dtt, 15.4, 12.1, 5.8)	–	–
6[b]	8.34 (s)	4.77 (d, 15.3)	3.62 (d, 15.3)	–	–	0.96 (s) 1.24 (s)	–
7	3.54[c] (s)	2.98 (dddd, 12.6, 4.6, 2.3, 1.3) 3.13 (dddd, 13.5, 4.6, 2.3, 1.3)	2.72 (ddd, 13.5, 12.3, 3.2) 2.84 (ddd, 12.6, 12.2, 3.3)	1.32 (ddddd, 13.4, 3.3, 3.2, 2.3, 2.3)	1.71 (ddddd, 13.4, 12.3, 12.2, 4.6, 4.6)	–	3.81[c] (s)
8	3.16[c] (s)	2.56 (dd, 10.8, 1.9) 2.68 (dd, 13.6, 1.9)	2.35 (d, 10.8) 2.49 (d, 13.6)	–	–	0.82 (s) 1.06 (s)	3.56[c] (s)
9	2.99 (d, 6.3) 3.61 (d, 6.3)	2.88 (ddd, 11.4, 8.9, 3.8) 3.07 (ddd, 13.4, 6.3, 4.1) 3.10–3.18 (m)	2.38 (ddd, ca. 11.4, ca. 11.4, 3.1) 2.72 (ddd, 13.3, 9.7, 5.9) 2.78 (ddd, 12.1, 8.9, 3.2) 2.66 (ddd, ca. 13.2, ca. 13.2, 3.5)	1.4–1.6 (m)	1.63–1.73 (m)	–	1.12 (d, 5.6) 3.48 (q, 5.6)
10	2.87 (d, 6.5) 3.52 (d, 6.5)	2.47 (dd, 11.4, 1.3) 2.61 (dd, 10.3, 2.0) 2.66 (dd, 13.5, 1.3) 2.67 (dd, 13.7, 2.0)	2.08 (d, 10.3) 2.46 (d, 13.5) 2.48 (d, 13.7) 2.54 (d, 11.4)	–	–	0.81 (s) 0.86 (s) 1.00 (s) 1.07 (s)	1.02 (d, 5.5) 3.42 (q, 5.5)
11	3.14 (s)	2.88 (dm, 10.8) 3.09 (ddm, 13.6, 4.6)	2.53 (ddd, 13.6, 12.3, 3.6) 2.57 (ddd, 11.4, 10.8, 3.1)	1.52 (ddddd, 13.0, 3.6, 3.1, 2.3, 2.3)	1.58 (dddd, 13.0, 12.3, 11.4, 4.6, 4.6)	–	1.01 (s)
12	3.11 (s)	2.40 (dd, 10.5, 2.1) 2.62 (dd, 13.6, 2.1)	2.31 (d, 10.5) 2.38 (d, 13.6)	–	–	0.80 (s) 0.94 (s)	1.03 (s)
13	3.68 (s)	2.98 (obscured) 3.15 (dddd, 13.5, 4.6, 2.3, 1.3)	2.73 (ddd, 13.5, ca. 12.5, 3.1) 2.78 (ddd, 12.6, 11.8, 3.2)	1.37 (dm, ca. 13.5)	1.68 (b m, obscured)	–	3.52 (d, 4.0) 3.89 (d, 4.0)
14	3.52 (s)	2.64 (obscured)	2.43 (d, 12.4)	–	–	0.76 (s) 1.09 (s)	3.44 (d, 4.1) 3.81 (d, 4.1)
15	3.83 (s)	obscured	obscured	1.35 (dm, ca. 13.0)	obscured	–	1.03 (d, 5.8) 4.15 (q, 5.8)
16	3.70 (s)	2.99 (ddm, 12.5 (8)) 3.17 (ddm, 13.4, 4.5)	2.72 (ddd) 2.77 (ddd)	(1.4–1.6 obscured)		–	0.93 (s) 1.27 (s)
17	4.71 (s)	3.16 (ddd, 15.0, 4.3, 2.1)	3.22 (ddd, 15.0, 12.6, 3.2)	0.91 (dtt, 13.7, 3.2, 2.1)	2.04 (dtt, 13.7, 12.6, 4.3)	–	3.61 (d, 2.2) 4.15 (d, 2.2)
18	4.56 (s)	2.75[c] (d, 13.4)	2.94[c] (d, 13.4)	–	–	0.93 (s) 1.14 (s)	3.94 (d, 2.6) 4.19 (d, 2.6)
19	4.81 (s)	3.17 (ddd, 14.7, 5.5, 2.4)	3.20 (ddd, 14.7, 11.0, 3.0)	0.89 (dtt, 13.5, 3.0, 2.4)	1.82 (dtt, 13.5, 11.0, 5.5)	–	1.01 (d, 5.0) 4.00 (q, 5.0)
20	4.78 (s)	2.76[c] (d, 13.8)	2.97[c] (d, 13.8)	–	–	0.92 (s) 1.09 (s)	1.06 (d, 5.1) 4.26 (q, 5.1)

[a] Spectrum of solution in $(CD_3)_2SO$. [b] Spectrum of solution in $(CD_3)_2CO$. [c] Signals may be interchangeable with others marked in the same way within the same row.

Bis(hexahydropyrimidines) 1 and 2 failed to react with acetone in methanol at room temperature. However, in the presence of ca. 0.1 equiv of acetic acid, formation of the trans 1:1 adduct 11 appeared to result from the reaction of 1 with 1 equiv of acetone in methanol at room temperature overnight. Under these conditions, the 500-MHz ^{1}H NMR spectrum of the crude product showed the presence of about 25% unreacted starting material 1. Several purification steps involving distillation and trituration with ether reduced the percentage of starting material but did not give a pure product. Attempts to crystallize the major product failed. Examination of the 500-MHz NMR spectrum of the product after distillation and trituration showed the major component to be the trans adduct 11 (75%), accompanied by starting material 1 (10%) and a third substance (15%), probably the cis 1:1 adduct 16. The addition of excess acetone failed to give any 1:2 adduct.

About 30% conversion of 2 into the trans 1:1 adduct 12, as estimated by low-field NMR spectroscopy, took place in refluxing methanol overnight. However, again in the presence of ca. 0.1 equiv of acetic acid, 2 reacted within 2 days with 1 equiv of acetone in methanol at room temperature to give 12, accompanied by some unreacted 2. The substrate 2 failed to react with excess acetone (up to 5 equiv) to give 1:2 adduct. Indeed the reaction of 2 with 5 equiv of acetone in methanol at room temperature over 2 days appeared to be the optimum conditions for the formation of the 1:1 adduct 12. Under these conditions the crude product comprised approximately 75–80% of the

adduct **12**, 6–7% starting material **2**, and approximately 10–15% of an unidentified product. Pure adduct **12** crystallized from the crude reaction product in modest yield (30%).

The unidentified product from the above reaction was also formed when only 1 equiv of acetone was reacted with **2** at room temperature. When **2** and acetone in a ratio of 1:5 were heated in methanol containing acetic acid to 70 °C overnight, a black tar was formed, comprising mainly the unknown compound but from which nothing could be distilled. The unknown substance had a simple NMR spectrum (δ 0.89 (s), 1.29 (s), 2.40 (s)) but could not be identified. Preparation of an authentic sample of one possibility, 2,2,5,5-tetramethylhexahydropyrimidine (**21**) (δ 0.81 (s), 1.21 (s), 2.58 (s)), revealed sufficient chemical shift differences in their spectra to make assignment uncertain. However, failure of the unknown to distill might mean that it was a low molecular weight polymer of the same composition as **21**. In any case it appears that the product arises through replacement of the glyoxal unit in **2** and the reaction was not pursued.

Reactions of Bis(hexahydropyrimidines) 1 and 2 with 2 Equiv of Formaldehyde and Acetaldehyde. The 1:2 adduct **17** from **1** was best prepared through treatment with formaldehyde, as formalin, in refluxing methanol overnight and was obtained after distillation in 40% yield. The reaction of **2** with 2 equiv of formaldehyde was studied under a variety of conditions, all of which resulted in the formation of a mixture of products in which the 1:2 adduct **18** was predominant. Formation of **18** appeared to be cleanest in refluxing ether overnight and gave, after double distillation of the crude product, a pure sample of **18** in 20% yield. No other major products could be isolated during the preparation of **17** and **18**.

The less substituted bis(hexahydropyrimidine) **1** reacted with acetaldehyde somewhat faster than did **2** to give the 1:2 adduct **8**. The reaction was essentially complete as indicated by NMR, after heating **1** with acetaldehyde (2 equiv) in methanol at 60 °C overnight. In contrast, the tetramethylbis(hexahydropyrimidine) (**2**) reacted smoothly only with an excess (2.9 equiv) of acetaldehyde at 60 °C in methanol. The reaction gave at first the 1:1 adduct **10** and then, after 2 days of heating, a crude product comprising over 90% of the 1:2 adduct **20**.

Structural Assignments of 1:1 Adducts 7–16 and 1:2 Adducts 17–20. Of all the 1:1 adducts **7–16**, only the trans isomers **7–10** and **12** could be isolated in crystalline form and even then **7** and **9** proved too deliquescent to obtain satisfactory elemental analyses. The mass spectra of **7–10** and **12** contained very small molecular ions (<1%) indicative of the 1:1 nature of the isolated adducts and the possible presence of the imidazolidine substructure. The structures of the minor isomers and proof of the stereochemistry of all the 1:1 adducts came from analysis of their ^{1}H NMR spectra (see Table IV).

The pairs of geminal proton signals from the imidazolidine rings of **7** and **8**, and the pair of methyl substituent signals of the same bridge of **11** and **12**, are each observed to be equivalent. This evidence strongly suggests a trans 4a,8b-ring junction in these molecules since this geometry should give rise to a 2-fold axis of symmetry in the molecules; the axis that bisects the 4a,8b-bond and passes through the bridging methylene carbon. Consistent with such trans geometry, compounds **7**, **8**, **11**, and **12** each showed equivalent signals for the protons at C4a and C8b.

A corollary to this prediction is that the singly methyl-substituted compounds **9** and **10** have neither an axis nor a plane of symmetry, because of their trans geometry. Hence, each of the protons of the methylene groups bound to nitrogen in their hexahydropyrimidine rings (a total of eight protons from each compound) resonates separately, as do the protons on C4a and C8b. The more remote methylene protons at C5 and C11 in **9** also resonate separately, as expected, although their signals are considerably overlapped. In the more highly substituted derivative, **10**, four well-separated methyl signals are observed, corresponding to the groups attached to C5 and C11. This nonequivalence of protons therefore provides powerful evidence for the assignment of trans geometry to the ring junction of these compounds.

^{13}C NMR spectroscopy supports the assignment of trans geometry to compounds **7–12** (see Table V). Only six signals were observed for the carbons of the 6-membered rings of compounds **7**, **8**, **11**, and **12**. This small number of signals arises due to the presence of the aforementioned axis of symmetry. Similarly, there were observed only two signals for the four methyl groups at C5 and C11 in compounds **8** and **12**. Compounds **9** and **10**, the less symmetrical trans 1:1 adducts, each gave eight signals for the carbons of the 6-membered rings, the maximum possible, and four signals for the C5, C11 methyl signals in **10**.

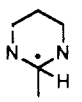
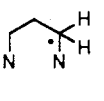
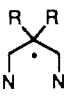
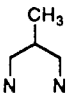
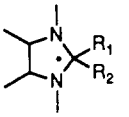
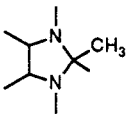
Assignment of the structures of compounds **13–16** was based solely on ^{1}H NMR evidence from impure (crude or semipurified) substances. The structures should therefore be regarded as tentative although the available evidence makes them highly probable.

Compound **13** showed seven resonance signals for the protons on the 6-membered rings (half the number of protons) and two signals for the bridging methylene protons (Table IV). The signals for $H1_{eq}$, $H2_{ax}$, and $H3_{eq}$ were partially obscured, which prevented accurate measurement of H1, H2, and H3 geminal and vicinal coupling constants, but the signal patterns for these protons (Table IV) were virtually identical with the corresponding signals from the trans isomer **7**. These results are entirely consistent with the proposed rigid, cis structure bearing a plane of symmetry that bisects the 4a,8b-bond and passes through the methylene bridge. A similar situation was noted for compound **14**. Subtraction of the ^{1}H NMR signals for **8** from the NMR spectrum of the distillate of the crude product allowed the assignment of structure **14** to the minor adduct, in which cis configuration about the 4a,8b-bond leads, as in **13**, to nonequivalence of the protons of the bridging methylene group.

Evidence for structure **15**, and to some extent **16**, was less compelling than for **13** and **14** because of severe overlap of some signals and our inability to detect others. Signals at δ 1.03 (d, J = 5.8 Hz), 3.83 (s), and 4.15 (q, J = 5.8 Hz) in the NMR spectrum of the crude product from **1** and acetaldehyde, at or above room temperature, indicated the possible presence of the cis 1:1-adduct **15**, with the second resonance assigned to the two equivalent protons H4a and H8b. Similarly, the minor signals that were visible and thought to be derived from **16**, from the reaction of **1** with acetone, were similar in chemical shift and splitting pattern to those of **13**. The major difference was the occurrence of two methyl signals in place of the nonequivalent methylene proton signals of **13**.

The ^{1}H and ^{13}C NMR spectra of the 1:2 adducts (Tables IV and V) provided good evidence of the highly symmetrical nature of structures **17–20**; their ^{1}H NMR spectra in particular confirmed their cis geometry about the central C–C bond. For example, compound **17** gave a ^{1}H NMR spectrum (Table IV) with seven signals, despite its 18 protons, and a ^{13}C NMR spectrum (Table V) with only four carbon resonances. The single fact that seven and not six

Table V. ^{13}C NMR Spectral Data of Compounds 1, 2, 7–12, and 17–20

						
1	73.8	45.2	27.2	22.9 26.3	–	–
2	73.6	57.3	29.5	–	–	–
7	78.2	44.2 46.8	23.1	–	68.2	–
8	79.0	57.4 60.6	30.3	25.0 26.4	71.2	–
9	75.0 75.5[a]	42.9 43.1 45.3 47.8	24.4 26.3	–	81.4[a]	16.9
10	74.9[a] 74.9	55.7 56.3 57.9 59.9	29.4 30.1	24.6 25.5 26.2 26.9	81.8[a]	16.6
11	72.3 (or 73.6)	43.9 45.1	27.1	–	75.2 (or 76.7)	23.5
12	77.2	56.0 57.6	30.2	24.0 26.3[a]	74.1	23.2[a]
17	76.5	43.8	14.1	–	70.1	–
18	75.9	55.9	29.7	28.8 29.5	75.2	–
19	75.1	42.9	14.9	–	71.0	18.7
20	73.7	54.6	29.3	29.0 29.1	77.8	18.4

[a] Signals may be interchangeable with others marked in the same way within the same row.

proton signals were observed for **17** indicated cis geometry. The cis isomer has two perpendicular planes of symmetry bisecting the molecule, while the trans isomer, which is less likely in any case because of the strain associated with the trans-5,5-ring fusion, has only one plane of symmetry, bisecting the molecule along its long axis, and a 2-fold axis of symmetry perpendicular to this plane. As a result, all four bridging methylene protons in the trans isomer should be equivalent thereby reducing the expected number of proton signals to six. The ^1H and ^{13}C NMR spectra of compounds **18–20** were simplified to the same extent and supported the stereochemical conclusions just described. The symmetry of **17** and **18** makes it impossible to distinguish between the cis and trans isomers by ^{13}C NMR spectroscopy. However, the spectra of **19** and **20** could only arise from the cis isomer thus they provide additional proof of the structures.

It is interesting to note that the geminal coupling constant for the bridging methylene protons in the cis bicyclic tetraamines, **13** and **14**, is 4.0 and 4.1 Hz while the same spin system in the cis tetracyclic compounds, **17** and **18**, show couplings of 2.2 and 2.6 Hz, respectively. A small geminal coupling constant for these protons is consistent with the small coupling which is typically observed for the corresponding position in dioxolanes (J = 0.2–1.2 Hz).[13] The significant reduction in coupling constant probably reflects the more rigid and slightly strained nature of the molecules brought about by the additional methylene bridge. A reduction in vicinal coupling constant from 5.8 to 5.0 Hz is also observed between the methine proton at the same bridging position and its adjacent methyl protons in **15** and **19**. There are also major changes in the chemical shifts of some protons in the hexahydropyrimidine rings of **13** and **14** when the ^1H NMR spectra are compared with those of **17** and **18**. For example, the equatorial protons adjacent to nitrogen in **17** resonate at δ 3.16. This is close to the chemical shift of the more downfield signal (δ 3.15) from the corresponding two nonequivalent, equatorial protons in **13**. Such a correlation is perhaps expected since the protons reside in similar positions relative to the rest of the molecule. However, the corresponding axial proton in **17** resonates at much higher chemical shift (δ 3.22) than either of the axial protons in **13**, δ 2.73 and 2.78. A pronounced upfield and downfield shift of the more remote equatorial and axial protons, respectively, of **17** compared with the shifts of the same protons in **13** is also observed.

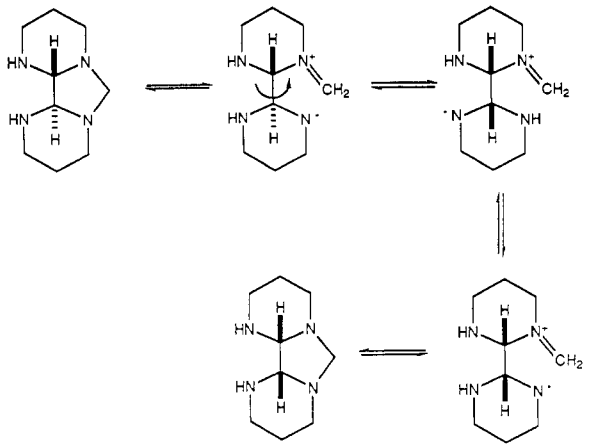
These observations add a level of sophistication to the earlier structural assignments of **13**, **14**, **17**, and **18**. They indicate that compounds **17** and **18** have very rigid structures with major 1,3-diaxial interactions that lead to the larger than expected increases in chemical shifts of the axial proton signals. By implication, compounds **13** and **14**, and probably **15** and **16**, have more flexible structures and are probably twisted from true chair conformations to minimise the 1,3-diaxial interactions.

Mechanistic Comments. The rates of the reactions of **1** and **2** with either 1 or 2 equiv of formalin varied with different batches of formalin used. This may be due to the presence of varying amounts of formic acid, known to be a contaminant in formalin. Acid catalysis was shown to be necessary in the reaction of **1** and **2** with acetone. Similar acid catalysis may have occurred also in reactions with glyoxal and acetaldehyde.

The condensation of formaldehyde, acetaldehyde, and acetone with bis(hexahydropyrimidines) **1** and **2** initially gave the trans 1:1 adducts, admixed in most cases with a lesser amount of the corresponding cis 1:1 adducts, in what presumably is a reversible reaction. The pathway leading to 1:2 addition products therefore could proceed through the trans or cis 1:1 adducts. The first possibility, that the 1:2 adducts arise from the addition of a second equivalent of aldehyde to a trans 1:1 adduct, giving a trans 1:2 adduct which then rapidly isomerizes, is unlikely because there is a high degree of strain associated with the trans 1:2 adducts. In addition, it has been reported that the tet-

(13) Anteunis, M.; Anteunis-De Ketelaere, F.; Borremans, F. *Bull. Soc. Chim. Belg.* **1971**, *80*, 701.

Scheme II



racyclic structure imparts relative hydrolytic stability to bis-aminals in the case of related tetracyclic tetraamines.[4] This makes it likely that intermediate trans 1:2 adducts would be detected if they are formed. As a consequence it is highly probable that 1:2 adducts are derived from the cis 1:1 adducts.

While interconversion of trans and cis 1:1 adducts might involve ring opening and reclosure of either the imidazolidine or tetrahydropyrimidine rings, the peripheral aminal groups of the 1:1 adducts should be more labile than the internal groups which are part of the 6-membered rings. Cleavage of the former would also increase the entropy of the molecules. Thus the following mechanism for conversion of the trans 1:1 adducts into the cis 1:2 adducts can be proposed (Scheme II).

Finally, it is intriguing to note that the skeletons of the trans and cis 1:1 adducts and of the cis 1:2 adducts can be derived from different conformations of the initial bis(hexahydropyrimidine) nucleus (Scheme III). This hypothesis and its consequences are under active investigation at present.

Experimental Section

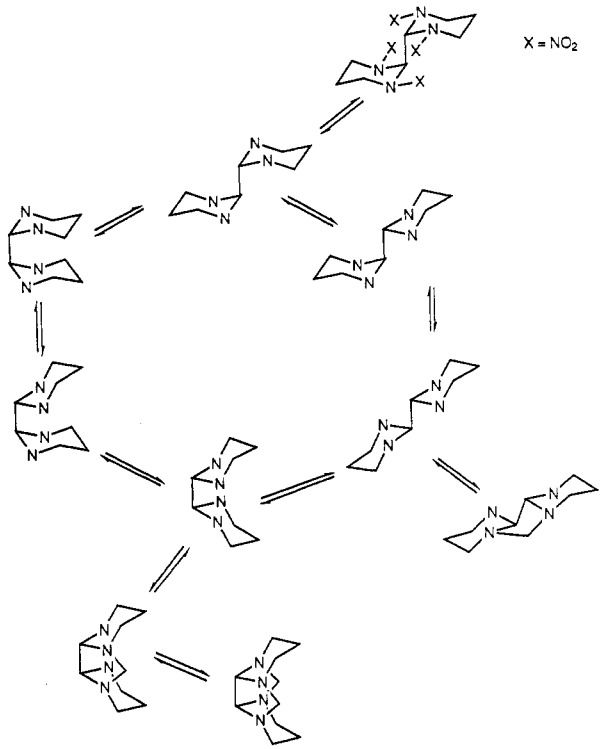
General. High vacuum (0.01 mm) and temperatures of 50–60 °C for several hours were required to dry analytical samples. Melting points were performed in sealed capillary tubes and are uncorrected. Microanalyses were performed by Dr. H. P. Pham of this school. Infrared spectra were recorded on Hitachi 260-10 or Perkin-Elmer 298 spectrophotometers. All IR show possible/probable H_2O, except for compound **9**, which was run during the summer. Unless otherwise specified NMR spectra were recorded as solutions in $CDCl_3$ at 500 MHz for ^1H and at 125.8 MHz for ^{13}C on a Bruker AM500 spectrometer. The mass spectra were measured on an AEI MS12 instrument.

Condensation of 1,3-Diaminopropane with Glyoxal. Aqueous glyoxal (40%, 181 g, 1.25 mol) was added dropwise to 1,3-diaminopropane (370 g, 5 mol) at 0 °C over 30 min. The mixture was heated on a steam bath for 3.5 h and then cooled in a refrigerator overnight. Filtration at the pump and then drying in vacuo gave pure **2,2′-bis(hexahydropyrimidine) (1)** as needles from 2-propanol: mp 120–122 °C (105 g, 49%); ^1H and ^{13}C NMR see Discussion; IR (KBr) 3300, 3230 (N–H + H_2O), 1640, 1500, 1425, 1310, 1295, 1225, 1185, 1110 and 995 cm^{-1}; mass spectrum, m/z (%) 170 (M^+, <1) and 85 (100). Anal. Calcd for $C_8H_{18}N_4$: C, 56.4; H, 10.7; N, 32.9. Found: C, 56.3; H, 11.0; N, 32.6.

Condensation of 1,3-Diamino-2,2-dimethylpropane with Glyoxal. Aqueous glyoxal (40%, 59 mL, 0.41 mol) was added dropwise with cooling in a water bath, over 15 min, to a solution of 1,3-diamino-2,2-dimethylpropane (102 g, 1.0 mol) in ethanol (20 mL). The mixture was heated on a steam bath for 3 h and cooled to room temperature overnight. The solid product (85.4 g) was filtered at the pump and dried in vacuo, mp 78–83 °C. Recrystallization from 2-propanol afforded **2,2′-bis(5,5-dimethylhexahydropyrimidine) (2)** as colorless needles (62 g, 75%): mp 95–96 °C; ^1H and ^{13}C NMR see Discussion; IR (KBr) 3200, 1640, 1440, 1370, 1340, 1290, 1100, 980 cm^{-1}; mass spectrum, m/z (%) 226 (M^+, 0.2) and 113 (100). Anal. Calcd for $C_{12}H_{26}N_4$: C, 63.7; H, 11.6; N, 24.75. Found: C, 63.4; H, 11.7; N, 24.35.

In one experiment, when the reaction mixture was not heated efficiently, another substance was also formed. The compound was separated from **2** as a powder in 5% yield during recrystallization. It was much less soluble and had a higher melting point, 208–211 °C, than **2**.

Scheme III



Nitrosation of Bis(hexahydropyrimidines) 1 and 2. General Procedure. The bis(hexahydropyrimidine) (10 mmol) was added portionwise to an ice-cold solution of $NaNO_2$ (3.5 g, 50 mmol) in water (25 mL), and the mixture was chilled to 0 °C. Hydrochloric acid (1 N, 50 mL) was added to the vigorously stirred mixture over 60 s. During this time the temperature rose to about 20 °C and there was much frothing. A fine precipitate separated, and the mixture was stirred for 30 min at 0 °C and then at room temperature for 1 h. The precipitate was collected, washed with cold water, and dried in air.

(a) 2,2′-Bis(1,3-dinitrosohexahydropyrimidine) (3). The crude product crystallized from aqueous dimethylformamide to give **3** as off-white prisms (36%); crystals darken and shatter above 230 °C, some sublime and darken 260–270 °C: ^1H NMR [$(CD_3)_2SO$] too complex a mixture to be assigned, see Discussion; IR (Nujol) 1490, 1455, 1370, 1355, 1340, 1310, 1280, 1235, 1190, 1090, 1060, 1035, 950, 910, 875, 755, 740 cm^{-1}; mass spectrum, m/z (%) 286 (M^+, absent), 143 (100). Anal. Calcd for $C_8H_{14}N_8O_4$: C, 33.6; H, 4.9; N, 39.2. Found: C, 33.75; H, 5.0; N, 37.8.

(b) 2,2′-Bis(1,3-dinitroso-5,5-dimethylhexahydropyrimidine) (4). The crude product (47%) crystallized from aqueous dimethylformamide to yield **4** as small off-white plates (26%): mp 280–295 °C dec; ^1H NMR [$(CD_3)_2SO$] too complex a mixture to be fully assigned, see Discussion; IR (Nujol) 1480, 1445, 1380, 1370, 1350, 1325, 1275, 1260, 1220, 1185, 1125, 1070, 1025, 990, 905, 870, 805, 720 cm^{-1}; mass spectrum, m/z (%) 342 (M^+, <1) and 171 (100). Anal. Calcd for $C_{12}H_{22}N_8O_4$: C, 42.1; H, 6.5; N, 32.7. Found: C, 42.0; H, 6.6; N, 32.5.

Nitration of Bis(hexahydropyrimidine) 1 and 2. General Procedure. Trifluoroacetic anhydride (75 mL) was placed in a 500-mL round-bottom flask, and the flask was cooled in a salt–ice bath to −5 °C. Fuming nitric acid (100%, 30 mL) was added dropwise over 20 min, and the mixture was allowed briefly to warm to room temperature and then recooled. The amine (50 mmol) was added cautiously in small portions over 10–20 min. The

mixture was then allowed to come to room temperature overnight. The resulting white precipitate was collected by vacuum filtration using a sintered-glass funnel under an atmosphere of nitrogen. The product was washed with dichloromethane and dried in air. The crude product was recrystallized in the following manner. The sample was dissolved in concentrated HNO_3 and then the solution was cooled slowly and trifluoroacetic acid added to dilute the solution. The supernatant was decanted from the precipitate, and more trifluoroacetic acid was added. The product was collected under suction and dried in vacuo.

(a) 2,2′-Bis(1,3-dinitrohexahydropyrimidine) (5). The crude product (26%) when recrystallized afforded **5** as colorless plates (13%): mp 280–287 °C dec; ^1H NMR [$(CD_3)_2SO$] see Table in Discussion; IR (KBr) 3020, 1540, 1520, 1440, 1350, 1320, 1285, 1240, 1190, 1130, 1110, 1030, 970, 930, 875, 845, 740, 705, 680 cm^{-1}; mass spectrum, m/z (%) 350 (M^+, absent), 175 (100), 129 (60), 99 (87), 84 (17), 83 (43), 72 (18), 56 (50), 55 (17). Anal. Calcd for $C_8H_{14}N_8O_8$: C, 27.4; H, 4.0; N, 32.0. Found: C, 27.2; H, 4.1; N, 31.7.

(b) 2,2′-Bis(1,3-dinitro-5,5-dimethylhexahydropyrimidine) (6). The crude product (15%) when recrystallized gave **6** as white flakes (9%): mp 270–280 °C dec; ^1H NMR [$(CD_3)_2CO$] see Table in Discussion; IR (KBr) 3020, 2970, 1550, 1450, 1370, 1340, 1270, 1180, 1170, 1140, 1070, 1020, 990, 960, 900, 875, 850, 770, 750, 730 cm^{-1}; mass spectrum, m/z (%) 406 (M^+, absent), 203 (100), 157 (20), 127 (22), 111 (22), 56 (17), 55 (13), 42 (24). Anal. Calcd for $C_{12}H_{22}N_8O_8$: C, 35.5; H, 5.5; N, 27.6. Found: C, 35.5; H, 5.5; N, 27.4.

Condensation of the Bis(hexahydropyrimidine) 1 with Formaldehyde. (a) With 1 Equiv of Formaldehyde. Formalin (40% w/v, May and Baker Analytical Reagent) (2.25 mL) was added to a solution of the bis(hexahydropyrimidine) **1** (5.1 g) in methanol (30 mL), and the solution was heated to 60 °C for 1 h. The solvent was evaporated in vacuo, giving a residue which was distilled on a Kugelrohr apparatus (110 °C, 0.2 mm). The distillate (2.4 g) was dissolved in ether (15 mL) and hexane (7 mL). The ether was allowed to evaporate overnight, giving the 1:1 adduct **4a,8b-*trans*-perhydro-4,5,8a,9a-tetraazafluorene (7)** (530 mg, 10%), as deliquescent needles: mp 91–94 °C (from ether/hexane); ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3300, 3200 (NH and H_2O), 1650, 1460, 1430, 1345, 1280, 1255, 1160, 1140, 1105, 915, 890 cm^{-1}; mass spectrum, m/z (%) 182 (M^+, <0.5) and 85 (100). Satisfactory microanalysis could not be obtained.

(b) With 2 Equiv of Formaldehyde. Formalin (7.5 mL) was added to a solution of the bis(hexahydropyrimidine) **1** (8.5 g) in methanol (100 mL), and the mixture was heated to reflux temperature overnight. The solvent was evaporated in vacuo, and the residue was distilled on a Kugelrohr apparatus (140 °C, 0.2 mm) giving the 1:2 adduct **8b,8c-*cis*-perhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorene (17)** (3.66 g, 38%): mp 111–114 °C (from ether); ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3200 (H_2O), 1460, 1445, 1380, 1360, 1345, 1290, 1275, 1175, 1125, 1070, 1040, 905 and 885 cm^{-1}; mass spectrum, m/z (%) 194 (M^+, 90), 193 (100), and 137 (100). Anal. Calcd for $C_{10}H_{18}N_4 \cdot {}^1/_3H_2O$: C, 60.0; H, 9.4; N, 28.0. Found: C, 59.9; H, 9.5; N, 27.8.

Condensation of the Bis(hexahydropyrimidine) 1 with Acetaldehyde. (a) With 1 Equiv of Acetaldehyde. Acetaldehyde (0.57 mL, 1.0 equiv) was added dropwise to a stirred solution of the bis(hexahydropyrimidine) **1** (1.7 g) in methanol (20 mL) at 0 °C. The solution was stirred for 1 h, and the solvent was evaporated in vacuo, the temperature being kept at 0 °C throughout. The residue was dried in vacuo at room temperature and then crystallized from ether/hexane, giving the 1:1 adduct **4a,8b-*trans*-9-methylperhydro-4,5,8a,9a-tetraazafluorene (9)** (1.0 g, 51%) as fine deliquescent needles: mp 68–76 °C; ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3300 (NH and H_2O), 1650, 1460, 1440, 1390, 1325, 1285, 1260, 1175 and 920 cm^{-1}; mass spectrum, m/z (%) 196 (M^+, 0.7) and 112 (100). Satisfactory microanalysis could not be obtained.

(b) With 2 Equiv of Acetaldehyde. Acetaldehyde (2.8 mL) was added to a solution of the bis(hexahydropyrimidine) **1** (3.4 g) in methanol (50 mL), and the mixture was heated to 55 °C overnight. The solvent was evaporated in vacuo, and the residue was distilled with a Kugelrohr apparatus (0.2 mm, 140 °C), giving the 1:2 adduct **4,8-*cis*-8b,8c-*cis*-4,8-dimethylperhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorene (19)** (2.83 g, 64%): mp 127–129 °C (from ether/hexane); ^1H and ^{13}C NMR see Tables in Discussion; IR (Nujol) 1340, 1260, 1200, 1170, 1140, 1000, and 860 cm^{-1}; mass spectrum, m/z (%) 222 (M^+, 1) and 112 (100). Anal. Calcd for $C_{12}H_{22}N_4$: C, 64.8; H, 10.0; N, 25.2. Found: C, 64.6; H, 10.25; N, 25.2.

Condensation of the Bis(hexahydropyrimidine) 1 with Acetone. A solution of the bis(hexahydropyrimidine) **1** (5 g), acetone (2.15 mL), and glacial acetic acid (0.15 mL) in methanol was stirred at room temperature overnight. The solvent was evaporated in vacuo at room temperature, and the residue was extracted with diethyl ether (50 mL). The ether extract was distilled twice by Kugelrohr distillation (140 °C, 0.1 mmHg), giving a distillate (1.4 g) which was dissolved in ether. The ether solution was reduced to 4–5 mL, giving a crystalline precipitate which was discarded. The ether-soluble fraction was distilled a third time by Kugelrohr distillation (120 °C, 0.05 mmHg) to yield a waxy semicrystalline solid (1.21 g, 20%), comprising mainly the adduct 9,9-dimethyl-4a,8b-*trans*-perhydro-4,5,8a,8b-tetraazafluorene (**11**), together with starting material **1** and a third substance which could not be identified. The product deliquesced rapidly on standing: ^1H NMR δ (for **11**) see Table in Discussion; δ (attributable to **16**) 0.93, 1.27 (2 s, 3 H each, 2 CH_3), 2.72, 2.77 (2 ddd, sum of coupling values = 29 Hz with same pattern as for δ 2.53 and 2.57 above, 2 H each), 2.99 (dm, J_{gem} = 12.5 Hz, $J_{vic\ +\ long\ range}$ = 8 Hz, 2 H), 3.70 (s).

Condensation of the Bis(hexahydropyrimidine) 2 with Formaldehyde. (a) With 1 Equiv of Formaldehyde. Formalin (0.75 mL, 1.0 equiv) was added to a stirred, cooled solution of the bis(hexahydropyrimidine) **2** (2.26 g) in methanol (20 mL), and the mixture was warmed to room temperature and then stirred for 1 h. The solvent was evaporated in vacuo at room temperature, and the residue was distilled with a Kugelrohr apparatus (150 °C, 0.2 mm). The distillate (930 mg, 39%) was dissolved in a little ether and hexane. The 1:1 adduct **4a,8b-*trans*-2,2,7,7-tetramethylperhydro-4,5,8a,9a-tetraazafluorene (8)** (200 mg, 8%) which crystallized from solution overnight was filtered and dried in vacuo: mp 86–90 °C (from ether/hexane); ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3300, 3200 (NH and H_2O), 1660, 1470, 1460, 1380, 1365, 1345, 1320, 1240, 1180, 1120, and 920 cm^{-1}; mass spectrum, m/z (%) 238 (M^+, 0.7) and 113 (100). Anal. Calcd for $C_{13}H_{26}N_4$: C, 65.5; H, 11.0; N, 23.5. Found: C, 65.35; H, 11.2; N, 23.3.

Subtraction of the ^1H NMR spectrum of **8** from that of the crude product afforded the spectrum of 4a,8b-*cis*-2,2,7,7-tetramethylperhydro-4,5,8a,9a-tetraazafluorene (**14**). For ^1H NMR see Table in Discussion.

(b) With 2 Equiv of Formaldehyde. Formalin (3 mL, 2.0 equiv) was added to a suspension of the bis(hexahydropyrimidine) **2** (4.5 g) in diethyl ether (50 mL), and the mixture was heated to reflux temperature for 1 h. The solution was cooled, the ether layer was separated and dried (sodium sulfate), and the solvent was evaporated, leaving a residue which was distilled with a Kugelrohr apparatus (145 °C, 0.03 mm). The distillate (1.815 g) was redistilled (140 °C, 0.1 mm), giving a pure fraction of the 1:2 adduct **8b,8c-*cis*-2,2,6,6-tetramethylperhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorene (18)** (1.26 g, 25%): mp 98–99 °C (from ether/hexane); ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3200 (H_2O), 1475, 1400, 1385, 1370, 1350, 1140, and 905 cm^{-1}; mass spectrum, m/z (%) 250 (M^+, 50) and 125 (100). Anal. Calcd for $C_{14}H_{26}N_4$: C, 67.15; H, 10.5; N, 22.4. Found: C, 67.0; H, 10.8; N, 22.4.

Condensation of the Bis(hexahydropyrimidine) 2 with Acetaldehyde. (a) With 1 Equiv of Acetaldehyde. Acetaldehyde (1.13 mL, 1.0 equiv) was added to a solution of the bis(hexahydropyrimidine) **2** (4.25 g) in methanol (50 mL) at 0 °C. The solution was warmed to room temperature and stirred for 1 h, and the solvent was then evaporated in vacuo at room temperature. The semicrystalline residue was heated with hexane (3 mL) and then cooled. The crystalline product **4a,8b-*trans*-2,2,7,7,9-pentamethylperhydro-4,5,8a,9a-tetraazafluorene (10)** (1.6 g, 34%) was filtered at the pump: mp 74–76 °C (from hexane). ^1H and ^{13}C NMR see Tables in Discussion; IR (Nujol) 3250 (NH and H_2O), 1295, 1235, and 1175 cm^{-1}; mass spectrum, m/z (%) 252 (M^+, 0.3), 251 (1.5), 250 (1), and 113 (100). Anal. Calcd for

$C_{14}H_{28}N_4$: C, 66.6; H, 11.2; N, 22.2. Found: C, 66.5; H, 11.5; N, 22.2.

(b) With 2 Equiv of Acetaldehyde. Acetaldehyde (1.8 mL) was added to a solution of the bis(hexahydropyrimidine) **2** (3.6 g) in methanol (40 mL). The solution was heated between 58 °C and 60 °C overnight and then cooled, a further aliquot (0.5 mL) of acetaldehyde was added, and heating was continued for a further 24 h. The solvent was evaporated in vacuo, and the residue was distilled on a Kugelrohr apparatus at 0.1 mm. A fraction (0.367 g) distilling at an oven temperature of 90–100 °C was discarded. The desired tetracyclic compound **4,8-*cis*-8b,8c-*cis*-2,2,4,6,6,8-hexamethylperhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorene (20)** distilled at 140 °C and solidified to a wax (2.57 g, 58%) on cooling: ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3200 (H_2O), 1660, 1470, 1390, 1380, 1350, 1340, 1325, 1240, 1180, 1150, 990, and 885 cm^{-1}; mass spectrum, m/z (%), 278 (M^+, 15) and 263 (100). Anal. Calcd for $C_{16}H_{30}N_4$: C, 69.0; H, 10.9; N, 20.1. Found: C, 68.7; H, 11.1; N, 20.0.

Condensation of Bis(hexahydropyrimidine) 2 with Acetone. A solution of the bis(hexahydropyrimidine) **2** (1 g), acetone (1.625 mL, 5.0 equiv), and glacial acetic acid (30 μL) in methanol was stirred at room temperature for 2 days. The solvent was evaporated in vacuo at room temperature, and the residue was extracted with hot diethyl ether (25 mL). The ether solution was reduced to 5 mL, hexane (ca. 5 mL) was added, and the solution was reduced to 7–8 mL. The resultant crystalline material was collected and found to be **2,2,7,7,9,9-hexamethyl-4a,8b-*cis*-perhydro-4,5,8a,8b-tetraazafluorene (12)** (0.33 g, 28%): mp 132–136 °C dec; ^1H and ^{13}C NMR see Tables in Discussion; IR ($CHCl_3$) 3300, 3150 (N–H, H_2O), 1640, 1460, 1380, 1370, 1355, 1320, 1280, 1265, 1255, 1180, 940, 920, 855 cm^{-1}; mass spectrum, m/z (%) 266 (M^+, 0.2) and 154 (100). Anal. Calcd for $C_{15}H_{30}N_4$: C, 67.6; H, 11.4; N, 21.0. Found: C, 67.3; H, 11.6; N, 20.8.

Preparation of 2,2,5,5-Tetramethylhexahydropyrimidine (21). A solution of 1,3-diamino-2,2-dimethylpropane (5.0 g, 0.05 mol) and acetone (3.6 g, 0.06 mol) in methanol (30 mL) containing glacial acetic acid (0.3 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the remaining clear liquid (5.2 g) was distilled to yield 2,2,5,5-tetramethylhexahydropyrimidine (**21**) as a colorless liquid: bp 70–73 °C (10 mmHg); ^1H NMR δ 0.81 (s, 2 CH_3), 1.21 (s, 2 CH_3), 1.40 (br s, NH), 2.58 (s, 2 CH_2); IR (KBr) 3420 (br), 3280 (br), 2320, 1605, 1480, 1435, 1390, 1375, 1330, 1235, 1170, 1093, 1025, 1000, 980, 920, 820, 730, 680, 650, 520, 450 cm^{-1}; mass spectrum, m/z (%) 142 (M^+, absent), 127 (71), 112 (34), 71 (100), 70 (73), 58 (69).

Crystallography. Crystal data for 5: $C_8H_{14}N_8O_8$, M 349.39, triclinic, space group $P\bar{1}$, a 6.602 (6) Å, b 7.341 (2) Å, c 8.231 (3) Å, a 89.54 (2), b 74.56 (2), g 66.15 (2)°, V 349.4 (2) Å^3, D_c 1.66 g cm^{-3}, Z 1, m_{Mo} 1.39 cm^{-1}. Crystal size 0.17 by 0.21 by 0.05 mm, $2\theta_{max}$ 50°, number of reflexions measured = 1220 with 957 considered observed. Final residuals R, R_w were 0.038, 0.051.

Structure Determination. Intensities were measured with an Enraf-Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode, using graphite monochromatized molybdenum radiation (10.7107 Å). Data were corrected for absorption. Reflexions with $I > 3s(I)$ were considered observed, and were used for full-matrix least-squares refinement after structure solution by direct phasing and Fourier methods. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located in difference Fouriers and given isotropic temperature parameters equivalent to those of the atoms to which bonded. Reflexion weights used were $1/s^2(F_o)$, with $s(F_o)$ being derived from $s(I_o) = [s^2(I_o) + (0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w = (SwD^2/SwF_o^2)^{1/2}$. Atomic scattering factors and anomolous dispersion parameters were from *International Tables for X-ray Crystallography*.[14] Structure solution was by MULTAN 80,[15] and refinement used BLOCKLS, a local version of ORFLS.[16] Cyber 172 and IBM3090 computers were used for all calculations.

An ORTEP drawing[17] of the structure showing the atom numbering is given in Figure 1. All bond distances, angles, and torsional angles are presented in Tables I–III.

Acknowledgment. This work was generously funded by the Australian Defence Science and Technology Organisation with the support of the Materials Research Laboratories, Melbourne, through research contract no. DST 85/17609.

Supplementary Material Available: Positional and anisotropic thermal parameters (2 pages). Ordering information is given on any current masthead page.

(14) *International Tables for X-ray Crystallography*; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. 4.

(15) Main, P. MULTAN 80; University of York: England, 1980.

(16) Busing, W. R.; Martin, K. O.; Levy, H. A. ORFLS; Oak Ridge National Laboratory: TN, 1962.

(17) Johnson, C. K. ORTEP-II; Oak Ridge National Laboratory: TN, 1976.